

II. REMARKS

Formal Matters

Claims 32-36 and 38-44 are pending after entry of the amendments set forth herein.

Claims 32-36 and 38-44 were examined and were rejected.

Claim 40 is amended. The amendment to claim 40 was made solely in the interest of expediting prosecution, and is not to be construed as acquiescence to any objection or rejection of any claim. No new matter is added by the amendment to claim 40.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Withdrawn rejections

Applicants note with gratitude that the following rejections, raised in the Office Action mailed May 5, 2006, have been withdrawn:

- 1) rejection of claim 40 under 35 U.S.C. §102(b) over Draper et al. (U.S. Patent No. 5,514,577; “Draper”);
- 2) rejection of claims 32, 33, and 35 under 35 U.S.C. §103(a) over Bennett et al. (WO 91/16901; “Bennett”) in view of Barsoum et al. (WO 94/04686; “Barsoum”); and
- 3) rejection of claims 42 and 43 under 35 U.S.C. §103(a) over Draper and Barsoum and further in view of Bennett.

Rejection under 35 U.S.C. §102(e)

Claims 40, 42, and 43 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Scholar et al. (U.S. Patent No. 5,552,390; “Scholar”).

The Office Action stated that Scholar teaches SEQ ID NO:14 DAN, d(P-thio) (CAGGGCTCTCATGGTGGC).

Claim 40 is amended to delete “AGGGCT.” Scholar neither discloses nor suggests any of the other sequences listed in claim 40. As such, Scholar does not anticipate claim 40, or any claim depending therefrom.

Rejections under 35 U.S.C. §103(a)

Claim 36 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bennett in view of Barsoum. Claims 40-43 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Scholar in view of Barsoum.

Claim 36 over Bennett in view of Barsoum

The Office Action stated that the rejection was maintained for reasons of record.

The May 5, 2006 Office Action stated:

1) Bennett teaches a nucleic acid of SEQ ID NO:12 (GGAAAGTTCCAGGGAAAGAGG), where the nucleic acid is in a pharmaceutically acceptable carrier;

2) Bennett teaches analogs encompassing phosphorothioate moieties;

3) Bennett differs by not conjugating to a peptide;

4) Barsoum teaches delivery of cargo molecules, such as nucleic acids, to the cytoplasm and nuclei by use of a transport polypeptide that comprises one or more portions of HIV tat protein which are covalently linked to cargo molecules.

The May 5, 2006 Office Action stated that it would have been obvious to conjugate the nucleic acid of Bennett to the transport peptides of Barsoum. Applicants respectfully traverse the rejection.

Bennett discusses antisense oligonucleotides. Bennett describes introducing antisense oligonucleotides into cells in medium alone or in medium containing DOTMA. Bennett, pages 30, 34, and 35; and Examples 1, 5, and 6. Bennett states that various antisense oligonucleotides reduced levels of 5-lipoxygenase significantly. Bennett, page 33, lines 32-35. There is no discussion in Bennett of

difficulty in getting the antisense oligonucleotides into cells. As such, there is no motivation provided in Bennett for conjugating an oligonucleotide to a cargo peptide.

Barsoum discusses use of a Tat polypeptide for cytoplasmic and nuclear delivery of biologically active non-tat proteins, nucleic acids and other molecules **that are not inherently capable of entering target cells or cell nuclei, or are not inherently capable of entering target cells at a useful rate.** Barsoum, page 5, lines 13-20.

Bennett does not characterize the antisense oligonucleotides discussed therein as “not inherently capable of entering target cells or cell nuclei,” or “not inherently capable of entering target cells at a useful rate.” As such, there would be no motivation in the cited references to combine the reference teachings. Accordingly, Bennett, alone or in combination with Barsoum, cannot render instant claim 36 obvious.

Claims 40-43 over Scholar in view of Barsoum

As discussed above, claim 40 is amended to delete “AGGGCT.” Scholar neither discloses nor suggests any of the other sequences listed in claim 40. As such, Scholar, alone or in combination with Barsoum, cannot render obvious claim 40, or any claim depending therefrom.

Conclusion as to the rejections under 35 U.S.C. §103(a)

Applicants submit that the rejection of claim 36, and the rejection of claims 40-43, under 35 U.S.C. §103(a) have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

Rejection under 35 U.S.C. §112, first paragraph

Claims 32-35, 38, 39, and 44 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action stated that the claims are drawn to pharmaceutical compositions and therefore the compositions must provide for treatment. The Office Action stated that "the alleged switch from a Th1 response to a Th2 response by the ISS-ODN autoantigen conjugate is not enabled to treat or prevent any autoimmune disease or specific diseases contemplated in the specification." Office Action, page 4. Applicants respectfully traverse the rejection.

Requirements to establish a case of lack of enablement

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis.¹ As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

The instant application provides ample enablement.

The instant specification provides ample description as to how to make and use an

The instant specification states that IIS reduce the immunostimulatory effect of ISS. Specification, page 7, line 4. The instant specification notes that ISS have been implicated in the onset and exacerbation of autoimmune disease. Specification, page 7, lines 22-24.

¹ *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)

The instant specification provides ample description of IIS. Specification, page 10, line 8 to page 13, line 11. The instant specification describes how to determine whether a given nucleic acid reduces the immunostimulatory effect of an ISS, and thus exhibits immunoinhibitory activity. Specification, page 8, line 17 to page 9, line 13; and Examples I-III.

The instant specification states that an IIS can be conjugated to an autoantigen or an autoantibody. Specification, page 18, lines 9-14; and page 18, line 14 to page 19, line 2. The specification describes various conjugation methods, a number of which were known in the art as of the priority date of the instant application. Specification, page 19, line 19 to page 20, line 2.

Finally, the instant specification provides ample description of how to administer an IIS or an IIS conjugate. Specification, page 21, line 1 to page 24, line 22. The instant specification provides a description of how to determine whether a Th2-type immune response has been induced. Specification, page 21, lines 11-16.

The instant specification provides working examples of the immunoinhibitory effect of a subject immunoinhibitory nucleic acid.

For example, Example I shows *in vitro* inhibition of ISS-stimulated proliferation of mouse splenocytes, by contacting ISS-stimulated splenocytes with IIS. Example II shows *in vitro* inhibition of ISS-stimulated production of IFN- γ by mouse splenocytes, by contacting ISS-stimulated splenocytes with IIS.

Example III shows *in vivo* induction of a Th2 immune response in mice. Mice were primed with the model antigen β -galactosidase (β -Gal) plus either an IIS or an ISS. Mice were subsequently challenged with β -Gal, and indicators of Th1 (e.g., IgG2a) and Th2 (e.g., IgE; IgG1) were measured. As shown in Figure 5, priming with IIS and β -Gal resulted in production of higher levels IgE when mice were challenged with β -Gal, compared to IgE levels produced by mice primed with ISS and β -Gal and challenged with β -Gal. In addition, as discussed in Example III, high levels of IgG2a antibodies (indicators of a Th1-type immune response) and low levels of IgG1 (indicators of a Th2-type immune response) were induced in response to β -Gal challenge in (ISS + β -Gal)-primed mice, while the low levels of IgG2a antibodies and high levels of IgG1 antibodies were induced in response to β -Gal challenge in (IIS + β -Gal)-primed mice.

Thus, the working examples provide both *in vitro* and *in vivo* evidence of the effect of IIS on inducing a Th2-type immune response.

Those skilled in the art would reasonably expect that an IIS conjugate would be at least as effective as an IIS in inducing a Th2-type immune response.

As noted above, the instant specification provides ample evidence that an IIS induces a Th2-type immune response *in vivo*. Those skilled in the art would reasonable expect that an IIS conjugate would be at least as effective as an IIS in inducing a Th2-type immune response.

The specification describes *in vivo* effects of ISS in inducing a Th1-type immune response. Specification, page 21, lines 11-12; and page 7, lines 12-14. It has been shown that ISS conjugated to an antigen elicits a more potent Th1 response to the antigen, compared to ISS administered alone or in admixture with the antigen. See, e.g., Cho et al. (2000) *Nat. Biotechnol.* 18:509-514; "Cho"; a copy of which is provided herewith as Exhibit 1. There is no reason to believe that an IIS, when conjugated to an autoantigen or autoantibody, would not be effective in inducing a Th2-type immune response.

The Office Action has not provided sufficient scientific rationale as to why one of ordinary skill in the art would not be able to make and use the invention as claimed.

1) The Office Action stated that the "ability to switch an antigen drive response when the antigen is conjugated to the inhibitory ODN has not been demonstrated." Office Action, page 5.

However, as noted above, the instant specification provides working examples of the immunoinhibitory effect of a subject IIS. As discussed above, evidence was provided that an IIS induces a Th2-type immune response *in vivo*, as evidenced by production of IgE antibodies and IgG1 antibodies, which are hallmarks of a Th2-type immune response.

Furthermore, all that is required is that an IIS conjugate as claimed be capable of inducing a Th2-type immune response in an individual. Applicants showed that an IIS induces a Th2-type immune response *in vivo*. There is no reason to believe that an IIS conjugate would not induce a Th2-type immune response. In fact, as noted above, there are ample scientific reasons why an IIS conjugate would induce a Th2-type immune response.

2) The Office Action stated that the art recognizes that genetic differences may contribute to control of the Th1/Th2 response.

However, the possibility that genetic differences may contribute to control of the Th1/Th2 response does not lead to a conclusion as to the enablement of claims 32-35, 38, 39, or 44.

3) The Office Action stated that the “administration of autoantigen conjugate in patients with autoimmunity would be expected to provide for stimulation of the already present and primed Th1 autoimmune response.” Office Action, page 5.

First, as noted above, Cho conjugated a model allergen to an ISS, and demonstrated that the ISS-model allergen conjugate induced a Th1-type immune response and reduced the level of IgE specific for the allergen. If it were true that administration of an IIS-autoantigen conjugate would provide for stimulation of the already present and primed Th1 autoimmune response, then one would also expect that the model allergen present in the ISS-model allergen conjugate of Cho would exacerbate an allergic response to the model allergen. Instead, the opposite occurred. Thus, there is no reason to expect that administration of autoantigen conjugate in patients with autoimmunity would provide for stimulation of the already present and primed Th1 autoimmune response.

Secondly, and as provided for under 37 C.F.R. §1.104(d)(2), Applicants invite the Office to provide an affidavit to support the assertion that “administration of autoantigen conjugate in patients with autoimmunity would be expected to provide for stimulation of the already present and primed Th1 autoimmune response.”

4) The Office Action stated that the failures of modulating existing autoimmune response using autoantigens are noted in the literature.

However, the instant claims do not recite autoantigens, or use of same for modulating an existing autoimmune response. Instead, claim 32-35, 38, 39, and 44 relate to IIS-autoantibody or IIS-autoantigen conjugates. Any disclosures of failures of modulating existing autoimmune response using autoantigens are not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

5) The Office Action stated that it is “well known in the art that antigen delivers both immunogenic and tolerogenic signals to lymphocytes”; and stated that the art teaches that obtaining the desired response with stimulation of antigen receptors with antigen is unpredictable “because many of these signals have both tolerogenic and immunogenic roles.” Office Action, page 5.

The possibility that an administered antigen might deliver both immunogenic and tolerogenic signals to lymphocytes is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44, as none of these claims recites an antigen or use of an antigen. Instead, claims 32-35, 38, 39, and 44 relate to IIS-autoantibody or IIS-autoantigen conjugates. As discussed in the instant specification, an IIS induces a Th2-type immune response; and an IIS-autoantigen conjugate induces a Th2-type immune response to an autoantigen.

6) The Office Action stated that “[t]here is no evidence of record that the conjugate inhibits, rather than exacerbating the ongoing established autoimmune response”; and that “[e]ven if one could switch to a Th2 response, the autoimmune disease still exists and moreover, the response is merely shifted to produce different isotypes of antibodies that could also be pathogenic.” Office Action, page 7.

First, as noted above, a subject IIS induces a Th2-type immune response. Also as noted above, those skilled in the art would find it reasonable to expect that, just as an ISS-allergen conjugate is efficacious in inducing a Th1-type immune response (thereby reducing an allergic response to the allergen), an IIS-autoantigen conjugate would induce a Th2-type immune response to an autoantigen.

Secondly, and as provided for under 37 C.F.R. §1.104(d)(2), Applicants invite the Office to provide an affidavit to support the assertion that “[e]ven if one could switch to a Th2 response, the autoimmune disease still exists and moreover, the response is merely shifted to produce different isotypes of antibodies that could also be pathogenic.”

The art cited in the Office Action does not lead to a conclusion of lack of enablement.

The Office Action stated that the specification “discloses that the method of the instant claims presumable treats Th1 autoimmune disease by administering an autoantigen or autoantibody conjugated to an ISS-ODN to skew the immune response towards Th1, from the Th1”; and stated that this “method is, again presumably, based on the theory that there exists a Th1/Th2 balance wherein increasing the Th1 or Th2 response decreases the other.” Office Action, bridging paragraph, pages 7-8. The Office Action cited various references; and stated that the art teaches that a Th1-Th2 cytokine switch or presence is not correlative of a therapeutic response. Applicants respectfully traverse.

First, instant claims 32-35, 38, 39, and 44 are not directed to methods; instead, they are directed to compositions.

Secondly, the art cited in the Office Action does not lead to a conclusion that instant claims 32-35, 38, 39, and 44 lack enablement.

The Office Action cited Louzoun et al. ((2001) *J. Autoimmunity* 17:311-321; “Louzon”); Brunet et al. ((2002) *Trends Immunol.* 23:127-128; “Brunet”); Genain et al. ((1996) *Science* 274:2054; “Genain”); and Hofstetter et al. ((2002) *J. Immunol.* 169:117-125; “Hofstetter”).

Louzon

The Office Action stated that many investigators consider the Th1/Th2 paradigm an overly simplistic way to view highly complex systems; and cited Louzon.

Louzon presents a model that is stated to explain both the general agreement and the apparently contradictory results described by various groups. Louzon actually supports the Th1/Th2 paradigm. As such, Louzon does not lead to a conclusion that claims 32-35, 38, 39, and 44 lack enablement.

Brunet

The Office Action stated that therapeutic manipulation of the Th1-Th2 balance is inherently dangerous and unpredictable; and cited Brunet.

However, Brunet does not discuss use of an IIS-autoantigen or IIS-autoantibody conjugate. As such, Brunet is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Furthermore, safety is not within the purview of the U.S. Patent Office; instead, safety considerations are within the purview of the U.S. Food and Drug Administration.

Genain

The Office Action stated that Genain teaches that immune deviation and shift of a cytokine production from a Th1 pattern to a Th2 pattern increased titers of autoantibodies, increase pathogenic autoantibodies and exacerbate autoimmune disease.

However, Genain discusses administration of myelin oligodendrocyte glycoprotein (MOG), which is said to be a minor constituent of myelin, to an experimental animal model of multiple sclerosis. Genain does not discuss use of an IIS-autoantigen conjugate. As such, Genain is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Hofstetter

The Office Action stated that the art teaches that autoimmune Th1 responses can develop and continue even in the presence and high frequencies of Th2 cells; and cited Hofstetter.

Hofstetter discusses administration of pertussis toxin (PT) to an experimental autoimmune encephalomyelitis (EAE) mouse, an experimental animal model of multiple sclerosis (MS). Hofstetter states that administration of PT to the EAE mouse prevented the protection from EAE conferred by injection of a peptide that induced a Th2 response. The purpose of the study was to assess the various effects of PT on the pathogenicity, cytokine differentiation, and clonal sizes of neuroantigen-reactive T cells in EAE in mice. Hofstetter does not conclude that inducing a Th2 response is not helpful in treating an autoimmune disorder. Hofstetter merely analyzed the effect of PT on the protection conferred by injection of neuroantigens. As such, Hofstetter does not lead to a conclusion that claims 32-35, 38, 39, and 44 lack enablement.

Hofstetter does not discuss use of an IIS-autoantigen conjugate. As such, Hofstetter is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Post-priority date references support the fact that claims 32-35, 38, 39, and 44 are enabled.

Others in the field recognize the usefulness of IIS in shifting an immune response from a Th1-type response to a Th2-type response; and recognize the usefulness of such a shift in, e.g., the treatment of autoimmune disorders.

Ho 2003

For example, Ho et al. ((2003) *J. Immunol.* 171:4920-4926; “Ho 2003”; a copy of which is provided herewith as Exhibit 2) discusses the use of an immunomodulatory GpG oligonucleotide in ameliorating autoimmune disease in an EAE mouse model of MS. Ho 2003 states that EAE is a Th1-mediated animal disease model of MS. Ho 2003, page 4920, column 2, second full paragraph. Ho 2003 states that the immunomodulatory GpG motif-containing oligonucleotide (IMO) stimulates the proliferation of Th2 cells. Ho 2003, page 4920, column 2, third full paragraph. Ho 2003 demonstrated that the IMO suppressed autoantigen-mediated EAE. Ho 2003, Figure 7; and page 4924, column 1, paragraph 1, to page 4925, column 2, paragraph 1.

Thus, Ho 2003 provides further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

Ho 2005

As another example, Ho et al. ((2005) *J. Immunol.* 175:6226-6234; “Ho 2005”; a copy of which is provided herewith as Exhibit 3) discusses the use of a mixture of autoantigen and an immunomodulatory GpG oligonucleotide (“GpG ODN”) to ameliorate autoimmune disease in an EAE mouse model of MS. Ho 2005 states that the immunomodulatory GpG-ODN counteracted the CpG-induced inflammatory effect in a Th1-mediated autoimmune disease by skewing both the autoaggressive T cell and B cell responses toward a protective Th2 phenotype. Ho 2005, Abstract.

Ho 2005 provides data showing that a combination of GpG ODN (IIS) and autoantigen shifted an immune response toward a Th2-type immune response, and resulted in amelioration of an autoimmune disorder. Those skilled in the art would reasonably expect that, as disclosed in the instant specification, an autoantigen-IIS conjugate would also shift an immune response toward a Th2-type immune response; and would therefore be useful in an autoimmune disease.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

In summary, the instant specification provides ample enablement for instant claims 32-35, 38, 39, and 44; the Office Action has not established lack of enablement of claims 32-35, 38, 39, and 44; and post-priority date art supports the fact that claims 32-35, 38, 39, and 44 are enabled.

Applicants submit that the rejection of claims 32-35, 38, 39, and 44 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §102(e)

Claims 40, 42, and 43 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Scholar et al. (U.S. Patent No. 5,552,390; “Scholar”).

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Applicants submit that the rejection of claims 40, 42, and 43 under 35 U.S.C. §102(e) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSD-173CON.

Respectfully submitted,
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